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Abstract

Introduction Type-2 diabetes mellitus is a key driver of cardiovascular disease often leading to renal failure, infarction or stroke. Here we investigate the role of Annexin-A1 (ANXA1), an endogenous anti-inflammatory peptide, in a mouse model of high-fat diet (HFD) induced insulin resistance and diabetic nephropathy.

Methods 10-week old male C57BL/6 (wild-type) and ANXA1 null ($ANXA1^{-/-}$) mice were fed a normal (chow) diet or high-fat high-sugar (HFD) diet for 10 weeks. Mice were administrated either human recombinant (hr) ANXA1 (1 μg hrANXA1, Hepes buffer, i.p.) or vehicle (100 μl Hepes buffer, i.p.) from weeks 5–10 of dietary manipulation.

Results When compared to WT-mice fed on chow diet, WT-mice fed on HFD exhibited significantly lower serum levels of ANXA1 (1.259±0.01 vs. 1.154±0.03 ng/ml, $P<0.05$) and reduced ANXA1 expression in the kidney (0.96±0.02 vs. 0.30±0.04 O.D, $P<0.05$). When compared to WT-mice fed on chow diet, WT-mice fed on HFD and subjected to OGTT demonstrated a significant impairment in their oral glucose tolerance test (OGTT; AUC analysis: 84.42±4.51 vs. 110.70±3.89, $P<0.05$), which was improved with hrANXA1 treatment (110.70±3.89 vs. 89.40±0.99, $P<0.05$). The OGTT of $ANXA1^{-/-}$ mice fed on HFD was significantly worse than that of WT-mice. When compared to WT-mice fed on chow diet, WT-mice fed on HFD demonstrated a significant increase in albumin-to-creatinine (ACR) ratio (20.75±2.434 vs. 56.10±5.80 mg/mg, $P<0.05$), suggesting the development of proteinuria, which was improved with hrANXA1 treatment (56.10±5.80 vs. 35.28±6.04 mg/mg, $P<0.05$). $ANXA1^{-/-}$ mice fed on HFD demonstrated a significant increase in ACR compared to WT-mice fed on HFD (56.10±5.80 vs. 79.38±4.33 mg/mg, $P<0.05$) suggesting more severe proteinuria. When compared to WT-mice fed on chow diet, WT-mice fed on a HFD had decreased phosphorylation Ser^{188} of RhoA in the liver (1.00±0.004 vs. 0.575±0.002 O.D, $P<0.05$) and kidney (0.95±0.02 vs. 0.030±0.04 O.D, $P<0.05$) which was associated with increased phosphorylation of MYPT1 (liver, 1.15±0.006 vs. 4.15±0.07 O.D, $P<0.05$; kidney, 1.025±0.09 vs. 2.60±0.09 O.D, $P<0.05$). Both of these signalling events was prevented by treatment with hrANXA1. Interestingly, $ANXA1^{-/-}$ mice demonstrated

constitutively activated RhoA and phosphorylation of MYPT1 suggesting that ANXA1 could be a major regulator of this GTPase activity.

Conclusion We have shown for the first time that ANXA1 expression is reduced in a mouse model of HFD-induced insulin resistance and diabetic nephropathy. This down-regulation removes an important tissue-protective factor allowing for exacerbation of renal dysfunction, which can be attenuated with treatment with hrANXA1. Most notably, hrANXA1 reduces both the metabolic derangements and the renal dysfunction associated with T2DM.

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